REMARKS/ARGUMENTS

Petition is hereby made under the provisions of 37 CFR 1.136(a) for an extension of one month of the period for response to the Office Action. Authorization to charge the prescribed fee to our deposit account is enclosed.

The entry of the Amendment of June 3, 2004 is gratefully acknowledged.

The Examiner noted that claims 19, 20, 22 and 24 to 26 were pending and that claim 21 was withdrawn from consideration, as a result of the species election.

The withdrawal of prior rejections with the exception of those stated in the Office Action also is gratefully acknowledged.

The Examiner required deletion of non-elected claim 21. This Amendment deletes such claim, such deletion being made without prejudice to applicants right, upon allowance of a generic claim, to consideration of claims to additional species which are written in dependent form or otherwise include the limitations of an allowed claim.

The Examiner objected to claims 19, 22 and 24 to 28 in view of the incorrect spelling of the word "promoter" in claim 19. This matter now has been corrected.

The Examiner objected to the disclosure as referring to US Patent Applications which had now issued to patent. The specification has now been amended in this respect to refer to the granted US Patents.

The Examiner rejected claim 24 under 35 USC 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention, with respect to the

recitation of a promoter. Having regard to the correction of the spelling of the term "promoter" in claim 1, it is submitted that there is adequate antecedent basis for the term "promoter" as used in claim 24. It is submitted that the rejection should be withdrawn.

The Examiner provisionally rejected claims 19, 22 and 24 to 28 under the judicially-created doctrine of obviousness-type double patenting as being unpatentable over claims 19, 20, 22 and 24 to 28 of copending Application No. 10/699,683.

As the Examiner notes, the rejection is a provisional one because the conflicting claims have not in fact been patented.

The Examiner rejected claims 19, 22 and 24 to 28 under 35 USC 103(a) as being unpatentable over Gurtiss III (US 5,389,368) taken with Brunham (WO 98/02546). Reconsideration of the rejection is requested having regard to the amendments made to claim 19 and the discussion contained herein.

Claim 19 is directed to an attenuated strain of a bacterium harbouring a vector comprising a nucleic acid molecule encoding a major outer membrane protein (MOMP) of a strain of Chlamydia and a promoter operatively coupled to the nucleic acid molecule for expression of the protein by cells of a host to which the attenuated strain is administered but not by the bacteria. In this regard, it is noted that the term "in a host" and "in the bacteria" have been amended to "by a host" and "by the bacteria" to further clarify the distinctions over the prior art.

The attenuated bacteria claimed herein are distinguished from the prior art in requiring that the promoter directs expression of the nucleic acid molecule by cells of a host to which the attenuated strain is administered but not by the attenuated strain itself. As described on page 8 of the specification, the expression of the DNA is effected when the bacterial vector has released the DNA into the

appropriate host cells. After uptake of the bacterial vector by the host cells, the auxotrophic bacterial dies after a few rounds of division due to their inability to synthesize the essential nutrients, such as amino acids or nucleotides. The plasmid DNA then is released into the cytoplasm in the host cell.

Gurtiss III provides a vaccine for immunization of a vertebrate or invertebrate comprising an avirulent derivative of a microbe. The derivative is substantially incapable of producing functional adenylate cyclase and cyclic AMP receptor protein while being capable of expressing a recombinant gene derived from a pathogen of the vertebrate or invertebrate to produce an antigen capable of inducing an immune response in the vertebrate or invertebrate against the pathogen (col. 3, ll. 42 to 50). Gurtiss III also disclose a method of stimulating the immune system of a vertebrate or invertebrate by administering the vaccine to the vertebrate or invertebrate (col. 3, line 60 to col. line 2).

Gurtiss III also describes a carrier microbe for the synthesis of a vertebrate or invertebrate host protein comprising the avirulent derivative of a pathogenic microbe which is capable of expressing a recombinant gene derived from a vertebrate or invertebrate host to produce a product capable of suppressing, modulating or augmenting an immune response to the vertebrate or invertebrate (col. 4, ll. 3 to 12).

It is clear from these passages that, in Gurtiss III, the avirulent microbe directs expression of the foreign antigen in the avirulent microbe. There is no disclosure in Gurtiss III of an avirulent microbe in which the foreign antigen is expressed by the host and not by the microbe, as required by applicants claims.

Thus, there is a fundamental difference between the attenuated bacteria defined in applicants claims defined therein and the cited prior art. In the present invention, the attenuated bacteria is employed as a carrier for the vector and it is the promoter in the DNA construct which directs expression of the *Chlamydia*

protein or fragment thereof by the host cells only and not by the attenuated bacteria, quite the reverse of Gurtiss III.

In the Final Action, the Examiner states:

> "Gurtiss III teaches an attenuated *Salmonella typhimurium* bacteria that is harboring a vector comprising heterologous nucleic acid molecule that encodes for a second pathogenic microorganism for example *C. trachomatis* (col. 6). Gurtiss teaches that the vaccine can be effective against bacterial disease agents such as *Chlamydia trachomatis* that causes venereal diseases and eye infections (col. 6). Incorporation of the recombinant nucleic acid molecule into the attenuated bacteria *(Salmonella typhimurium)* is accomplished through the use of plasmid, phage or cosmid vectors (col. 11; col. 6; claims). "The recombinant DNA is packaged within a phage such as transducing phage or cosmid vectors. Once the recombinant DNA is in the carrier cell, it may continue to exist as a separate piece (generally true of complete transmitted plasmids) or it may insert into the host cell chromosome and be reproduced with the chromosome during cell division." (col. 11). Gurtiss teaches the claimed invention except for the specific a nucleic acid molecule encoding a MOMP from *C. trachomatis,* that the promoter is a cytomegalovirus promoter and the plasmid vector pcDNA3/MOMP."

It is submitted that the conclusion drawn by the Examiner is not supported by the disclosure of Gurtiss III.

It is agreed with the Examiner that the avirulent microbes preferably are derived from *Salmonella* (col. 6, ll. 12 to 15) and that *Chlamydia* is identified as a pathogenic microorganism useful in Gurtiss III constructs (claim 6 and also in col. 6, ll. 52 to 53). However, Gurtiss III states, in col. 6, ll. 16 to 34:

> "In another embodiment of the invention, the avirulent derivative of a pathogenic microbe also referred to herein as a carrier bacteria can be used to deliver selected antigens to the GALT ..... If these carrier bacteria contain and express a recombinant gene from a pathogenic organism, antibodies against the antigenic gene product produced from the pathogen will. be induced. With the advent of recombinant

> DNA techniques, it now becomes possible to develop totally unique vaccines in which specific antigens are produced, not by the etiologic agent, but by another host strain of bacteria capable of expressing the gene for that antigen." (Emphasis added).

It is absolutely clear from this passage that Gurtiss III is contemplating expression of the foreign gene by the avirulent bacteria. In addition, Gurtiss III defines the term "expression of a gene" as:

> "Expression of a gene means that the information inherent in the structure of the gene is transformed into a physical product ... by the biochemical mechanisms of the cell. in which the gene is located." (Emphasis added) (col. 9, ll. 37 to 43)

The patentee elaborates on the use of the avirulent microbe as a carrier (in col. 10, ll. 10 to 24):

> ".....once the carrier microbe is present in the animal, the antigen needs to become available to the animal's immune system. This may be accomplished when the carrier microbe dies so that the antigen molecules are released. ... In this way, it is possible to use a viable microbe that will persist in the vaccinated animal, for example, in the Peyer's patches and continue to produce antigen, thereby continually inducing antibody formation." (Emphasis added)

It is clear, therefore, that Gurtiss III contemplates only expression of antigen by the carrier avirulent microbe. The reference contemplates no production of antigen following death of the carrier microbe. Any antigen is produced only by the avirulent microbe, even after uptake by the Peyer's patches.

Accordingly, in addition to the features noted by the Examiner, the Gurtiss III reference does not disclose or suggest the feature of claim 19, that the Chlamydia protein is expressed by the cells of the host to which the attenuated strain is administered but not by the attenuated bacteria. In the Gurtiss III, the foreign protein is expressed by the attenuated bacteria.

The Examiner goes on to say in the Final Action that:

> "However, Brunham teaches DNA immunization against Chlamydia infection comprising nucleic acid, including DNA, immunization to generate a protective immune response in a host, to a major membrane protein of a strain of Chlamydia *(C. trachomatis)*, preferably contains a nucleotide sequence encoding a MOMP that generates antibodies that react with MOMP and a promoter sequence operatively couples to the first nucleotide sequence for expression of the MOMP in the host (abstract; p. 3; pp. 20 to 21 Example 4). The non-replicating vector may be formulated with a pharmaceutically acceptable carrier for in vivo administration to the host (abstract; p. 3). Brunham teaches that the promoter may be the cytomegalovirus promoter-and that the non-replicating-vector maybe plasmid pcDNA3 into which the nucleotide sequence is inserted (i.e. pcDNA3/MOMP) (pp. 4 to 5; p. 8). The plasmid vector containing the MOMP gene from *Chlamydia trachomatis* was pcDNA3 with transcription under control of the human cytomegalovirus promoter (pp. 16 to 7; p. 25, Table 2; claims). The prior teaches the use of the promoters and vectors for expression of the Chlamydia MOMP for protecting a host against Chlamydia infection."

The applicants agree with the Examiner's characterization of the teachings of Brunham. Brunham describes a vector comprising a nucleic acid sequence encoding a MOMP or MOMP fragments and a promoter sequence operatively coupled to the MOMP sequence for expression of the MOMP in the host and the production of an immune response to the MOMP upon administration of the vector to the host. As the Examiner observes, the Brunham reference is concerned with DNA immunization. It is noted that the earliest date of filing of Gurtiss III (June 1987) predates any notion of DNA immunization to effect foreign gene expression by a host to which an expression vector is administered. It is believed that Ulmer et al (1993, ref. 39 herein) is the earliest paper contemplating DNA immunization.

The Examiner further states in the Final Action that:

> "It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the attenuated *Salmonella typhimurium* bacteria of Gurtiss to include harboring a nucleic acid molecule encoding a Chlamydial protective MOMP of Brunham because Gurtiss teaches that through administration of a live

> attenuated bacteria that encodes a protective protein a host is stimulated to produce an immune response directed against the expressed gene product and with a subsequent administration of purified protein, an enhanced secretory immune response is obtained." (emphasis added)

It is submitted that, while Brunham may suggest that the foreign gene in Gurtiss III may be MOMP, the fact remains that such a combination does not provide the attenuated bacteria claimed in claim 19. The Examiner's attention again is directed to col. 10, ll. 10 to 24 of Gurtiss III which refers to the manner of introduction of antigen to the host. It is abundantly clear that it is the attenuated microbe which expresses the antigen, such as MOMP. It is submitted that applicants claim language in claim 19 clearly distinguishes over the combination of Gurtiss III and Brunham:

> "An attenuated strain of a bacterium harboring a vector comprising a nucleic acid molecule ... and a promoter operatively coupled to said nucleic acid molecule for expression of said protein by the cells of the host..... but not by said attenuated bacteria" (emphasis added).

In Gurtiss III, the antigen is always produced by the attenuated bacteria.

The Examiner further states in the Final Action that:

> "The person of ordinary skill in the art would have been motivated by the reasonable expectation of success of obtaining an attenuated *Salmonella typhimurium* bacteria that comprises the nucleic acid, plasmid and promoter of Brunham that encodes a protective MOMP of *Chlamydia trachomatis,* because Gurtiss teaches that Chlamydia is a pathogen that causes venereal diseases and eye infections. The attenuated bacteria is capable of expressing a recombinant gene product, wherein use of a nucleic acid molecule that encodes a protective MOMP results in stimulating an immune response against the *Chlamydia trachomatis* MOMP." (Emphasis added)

It is submitted that, while there may be motivation to use the MOMP gene in the attenuated microbe of Gurtiss III, the combination of prior art lacks any motivation to utilize the promoter of Brunham along with the nucleic acid molecule encoding

MOMP. As the Examiner states, in Gurtiss III, the attenuated bacteria is capable of expressing a recombinant gene product. For such purpose, Gurtiss III uses a promoter functional in the attenuated microbe. Brunham is quite different, in that the promoter is functional in the cells of the host to whom the vector is administered. In applicants invention, the promoter is functional in the cells of the host to which the vector is administered and not in the cells of the attenuated bacteria.

To replace the promoter of Gurtiss III by the promoter of Brunham would result in an attenuated bacteria which does not function in the manner required by the teaching of Gurtiss. Thus, the foreign antigen would not be expressed by the attenuated bacteria. Accordingly, it is submitted that there is no motivation to a person skilled in the art to replace the promoter in Gurtiss III by that of Brunham.

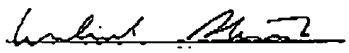
Accordingly, it is submitted that claims 19, 22 and 24 to 28 are patentable over the applied combination of prior art and hence the rejection thereof under 35 USC 103(a) as being unpatentable over Gurtiss III taken with Brunham, should be withdrawn.

Entry of this Amendment after Final Action is requested, in that the application thereby is placed in an allowable form. In the event the Examiner considers one or more ground of rejection to remain, the Amendment nevertheless should be entered since the issues for consideration on appeal thereby are reduced and/or the claims are placed in better condition for appeal.

In the event the Examiner considers that further modification to the claim language is desirable to define the patentable subject matter thereof, the Examiner is requested to call the undersigned, Mr. Michael Stewart, collect, at the number given below, in order to arrive at mutually-acceptable language.

It is believed that this application is now in condition for allowance and early and favourable consideration and allowance are respectfully solicited.

Respectfully submitted,



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